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Patentanmeldung Nr. Patent application No. Demande de brevet n°

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Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

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R C van Dijk

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Direct compressible trehalsoe solids

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CER03-0004

Direct Compressible Trehalose Solids

Technical Field

The present invention relates to direct compressible crystalline or semi-crystalline trehalose solids and a process for preparing it.

Background of the invention

Trehalose (α-D-glucopyranosyl-α-D-glucopyranoside) has been known from ancient times as non-reducing saccharide composed of glucose. It is found for example, in micro-organisms such as in fungi and in certain yeasts. It is also found in insects, mushrooms and in certain drought-resistant plants. It can be manufactured by fermentation of certain strains of yeast. Trehalose is sweet-tasting and has been suggested for use as a sweetener having reduced cariogenicity in chewing gum and the like. Furthermore, trehalose demonstrates satisfactory pH- and thermal-stabilities.

WO97/28788 describes tablets comprising a major fraction of trehalose as a diluent or excipient. The resulting tablets can be used as vehicles for oral administration of therapeutic substances. The tablets may be produced by direct compression.

GB 2,353,933 provides a sugar composition for tableting by direct compression, comprising a minor fraction of particulate trehalose in combination with a major fraction of one or more substances that are not in themselves sufficiently directly compressible to form tablets having high integrity.

JP2001-213890-A relates to improvement of the fluidity of a trehalose and improving compression-molding properties by controlling the physical property of trehalose.

There is a further need for having trehalose solids with improved compressibility properties.

The current invention provides such a product and a process for preparing it.

Summary of invention

The current invention relates to crystalline or semi-crystalline trehalose solids characterized in that

a) Said solids have a specific surface area greater than 0.25 m^2/g, preferably greater than 0.30 m^2/g, more preferably a specific surface area of at least 0.40 m^2/g, and
b) Said solids contain a crystal type selected from the group consisting of trehalose dihydrate and mixtures of trehalose dihydrate and anhydrous trehalose.

The current invention relates to trehalose solids having an average particle size greater than 100µm.

Furthermore, the current invention relates to a process for preparing crystalline or semi-crystalline trehalose solids containing having a specific surface area greater than 0.25 m/g^2, and containing a crystal type selected from the group consisting of trehalose dihydrate and mixtures of trehalose dihydrate and anhydrous trehalose and said process is comprising the following steps:

a) Heating a solution of trehalose above temperature of solubility,
b) Applying shear and cooling for obtaining trehalose solids, and
c) Optionally drying of trehalose solids.

In particular, said solution of trehalose in step a) is an aqueous solution and is prepared from trehalose and at least 5% water, based on dry substance of trehalose, is added. In addition, in said process the temperature of solubility is at least 80°C.

The trehalose solids of the current invention are used in food applications, pharma applications or cosmetics.

The current invention further relates to the use of said trehalose solids as cryoprotectant, as carrier, as binder in tablet formation or said solids are the integral part of the tablets.

Furthermore, the current invention relates to tablets containing crystalline or semi-crystalline trehalose solids having a specific surface area greater than 0.25 m^2/g, and containing a crystal type selected from the group consisting of trehalose dihydrate and mixtures of trehalose dihydrate and anhydrous trehalose and wherein said tablets have a

tensile strength of at least 4 N/mm^2, preferably of at least 6 N/mm^2, more preferably more than 7 N/mm^2.

Description of the figures

Figure 1: DSC thermogram for trehalose solids comprising two crystal types. The DSC thermogram (heating rate 5°C/min, hermetically closed DSC pan) shows that the material is completely crystalline (no Tg). Both dihydrate and anhydrous crystals are present.

Figure 2: graph with tensile strength of tablets prepared with trehalose solids. Tensile strength is expressed in function of increasing compression force.

Figure 3: graph with tensile strength of tablets prepared with trehalose solids and compared with tensile strength of tablets prepared with physical blend of trehalose dihydrate and anhydrous trehalose (same ratio).

Detailed invention

The current invention relates to crystalline or semi-crystalline trehalose solids characterized in that

a) Said solids have a specific surface area greater than 0.25 m^2/g, preferably greater than 0.30 m^2/g, more preferably a specific surface area of at least 0.40 m^2/g, and

b) Said solids contain a crystal type selected from the group consisting of trehalose dihydrate and mixtures of trehalose dihydrate and anhydrous trehalose.

Trehalose solids having a specific surface area of 0.70 m^2/g and more are obtainable.

The current invention can use α,α-trehalose, α,β-trehalose and β,β-trehalose as raw material. However, the natural occurring α,α-trehalose is preferred.

The trehalose solids in accordance with the invention exhibit a high specific surface area with nevertheless a low hygroscopicity.

The trehalose solids of the current invention have much better properties then existing trehalose in solid form and these properties are due, at least in part to the particularly high specific surface area of this product.

The two crystal types, that might be present in the solids, correspond to trehalose dihydrate and anhydrous trehalose. The ratio of trehalose dihydrate and anhydrous

trehalose is from 100/0 to 10/90, preferably from 80/20 to 20/80 more preferably said ratio is from 60/40 to 40/60. The properties of these trehalose solids are significant different than the properties of a traditional (physical) blend of trehalose dihydrate and anhydrous trehalose. The trehalose solids of the current invention profit from a kind of synergistic effect resulting in superior properties such as direct compressibility, lower hygroscopicity than anhydrous trehalose, and improved flowability in comparison to amorphous trehalose.

The current invention relates to trehalose solids having an average particle size greater than 100μm. If the particle size is smaller than 100μm, then the adhesion cohesion of the particles increases and the fluidity deteriorates. The trehalose solids of the current invention exhibit an excellent flow grade.

The current invention relates to a process for preparing crystalline or semi-crystalline trehalose solids containing a crystal type selected from the group consisting of trehalose dihydrate and mixtures of trehalose dihydrate and anhydrous trehalose and, having a specific surface area greater than 0.25 m^2/g, and said process is comprising the following steps:

a) Heating a solution of trehalose above temperature of solubility,

d) Applying shear and cooling for obtaining trehalose solids, and

b) Optionally drying of trehalose solids.

Temperature of solubility is temperature where there are no longer solid particles of trehalose in the solution and solution is becoming transparent.

Trehalose can solubilise in any liquid medium, preferably trehalose is solubilised in water. The aqueous solution can be prepared from trehalose and at least 5% water, based on dry substance of trehalose, is added. Such a solution has a temperature of solubility of at least 80°C.

Applying shear is essential for obtaining trehalose solids containing a crystal type selected from the group consisting of trehalose dihydrate and mixtures of trehalose dihydrate and anhydrous trehalose and, having a specific surface area greater than 0.25 m^2/g.

Furthermore, the current invention relates to the use of said trehalose solids in food applications, pharma applications or cosmetics. In fact, the trehalose solids of the

current invention can be used in health food, as bath agent, animal medicine, a diagnostic, an agrochemical, and as a fertilizer and any other application which can benefit from the improved properties of the trehalose solids of the current invention.

In particular, the trehalose solids of the current invention can be used as cryoprotectant, as carrier, as binder in tablet formation or said trehalose solids can be tabletted as such without the addition of any active ingredient. Tablets can be applied in food, feed and/or pharma applications.

Furthermore, the current invention relates to tablets containing crystalline or semi-crystalline trehalose solids having a specific surface area greater than 0.25 m^2/g, and containing a crystal type selected from the group consisting of trehalose dihydrate and mixtures of trehalose dihydrate and anhydrous trehalose and wherein said tablets have a tensile strength of at least 4 N/mm^2, preferably of at least 5 N/mm^2, more preferably more than 7 N/mm^2.

The tensile strength of tablets can be expressed in function of compression force (see figure 2).

Because of its high compressibility, the mechanical strength of the tablets obtained with the trehalose solids of the current invention is indeed particularly high, in comparison with that of the tablets obtained with the commercial products. There is also a significant difference between the properties of the tablets prepared with the current disclosed trehalose solids and the properties of tablets prepared with physical blends of trehalose dihydrate and anhydrous trehalose (see comparative example).

As a lubricant agent in tablet formation, magnesium stearate, calcium stearate, stearic acid, sucrose fatty acid esters, talc etc. can be applied.

The current invention has the following advantages:

- Due to presence of a crystal type selected from the group consisting of trehalose dihydrate and mixtures of trehalose dihydrate and anhydrous trehalose, the trehalose solids are less hygroscopic than anhydrous trehalose and have improved storage stability.
- Trehalose solids of current invention show good flowability.
- Trehalose solids with such increased specific surface area are suitable for direct compressibility

- Tablets prepared from trehalose solids of current invention have excellent tensile strength properties

The current invention is illustrated by way of the following examples.

Examples

Preparation of trehalose solids.

Trehalose dihydrate (Treha® HS) was dissolved at 80% dry substance in hot water (taking into account the crystal water).

The aqueous solution was treated in pilot Readco extruder with the following operation parameters:

Speed of pump: 29rpm

Speed of Readco: 50 rpm

Product feed: 53 kg/h

Inlet temperature: 99°C

Outlet temperature: 38°C

Cooling water inlet: 14°C

Cooling water outlet: 23°C

Crystallisation of the product was easy and the obtained strings or flakes were dried at 25°C and 30% RH in a climate chamber. After drying the strings were broken, milled and sieved over 500 µm sieve for obtaining trehalose solids.

Thermograms by DSC show the presence of two crystal types (see Figure 1). The melting of dihydrate crystals starts at 94°C and is followed by the melting of anhydrous crystals. The melting point of anhydrous crystals is depressed by crystal water freed during melting of the dihydrate crystals since the DSC measurement was done in a hermetically closed DSC pan.

Further physico-chemical properties are displayed in Table 1 .

Table 1:

Density	g/cm^3	0.61
Moisture (free and crystal water)	%	9.1
Specific surface	m^2/g multiple	0.32
Flodex Flowability		30
Mean particle size	µm	275

Tabletting

The milled and sieved product of the Readco treatment was applied for preparing tablets on the Fette tablettizer, (Type Perfecta 1000), and 22 punches were used. The material was compressed at a speed of 20.000 tablets/h. The tablets had a diameter of 1.1cm and a weight of 350mg.

1% magnesium stearate based on dry substance of trehalose solids was added. The product was mixed for 3 minutes in a low shear rotating tubular mixer (Twist PBI 10975) and applied on the Fette tablettizer.

The properties of the prepared tablets were evaluated by measuring their tensile strength as a function of the compression force. The tensile strength was measured with a Checkmaster (see Figure 2).

In figure 2 the tensile strength of Readco extruded trehalose solids is depicted as a function of the compression force. A plateau value is reached at 15kN compression force.

Comparative Example

Physical Blends of trehalose dihydrate and anhydrous trehalose

A physical blend of 66% dihydrate (Treha® HS) and 33% anhydrous trehalose (HS) was made by mixing the two powders in a low shear rotating tubular mixer (Twist PBI 10975) for 10min. After addition of 1% magnesium stearate based on dry substance of physical blend, the product was mixed for another 3min.

350mg tablets were made on a Fette tablettizer, using the same set-up as in example 1. The properties of the prepared tablets were evaluated by measuring their tensile strength as a function of the compression force.

The tensile strength of tablets made from Readco extruded trehalose solids and tablets made from a physical blend of dihydrate and anhydrous trehalose crystals, were compared. The ratio of anhydrous versus dihydrate crystals was similar in both tests (see Figure 3).

In figure 3 it is shown that the tensile strength of the tablets prepared with the physical blends is much lower than the tensile strength of the tablets prepared with the trehalose solids of the current invention.

Claims

1. Crystalline or semi-crystalline trehalose solids characterized in that
   a) Said solids have a specific surface area greater than 0.25 m^2/g, preferably greater than 0.30 m^2/g, more preferably a specific surface area of at least 0.40 m^2/g, and
   b) Said solids contain a crystal type selected from the group consisting of trehalose dihydrate and mixtures of trehalose dihydrate and anhydrous trehalose

2. Trehalose solids according to claim 1 characterised in that said solids have an average particle size greater than 100µm.

3. A process for preparing crystalline or semi-crystalline trehalose solids having a specific surface area greater than 0.25 m^2/g, and containing a crystal type selected from the group consisting of trehalose dihydrate and mixtures of trehalose dihydrate and anhydrous trehalose and containing, and said process is comprising the following steps:
   a) Heating a solution of trehalose above temperature of solubility,
   b) Applying shear and cooling for obtaining trehalose solids, and
   c) Optionally drying of trehalose solids.

4. A process according to claim 3 characterised in that in step a) solution of trehalose is an aqueous solution.

5. A process according to claim 4 characterised in that said aqueous solution is prepared from trehalose and at least 5% water based on dry substance of trehalose.

6. A process according to anyone of claim 3 to 5 characterised in that temperature of solubility is at least 80°C.

7. Use of crystallization or semi-crystallisation trehalose solids containing a crystal type selected from the group consisting of trehalose dihydrate and mixtures of trehalose

dihydrate and anhydrous trehalose and having a specific surface area greater than 0.25 m^2/g, in food applications, pharma applications or cosmetics.

8. Use according to claim 7 characterised in that said trehalose solids are applied as cryoprotectant.

9. Use according to claim 7 characterised in that said trehalose solids are applied as carrier.

10. Use according to claim 7 characterised in that said trehalose solids are applied as binder in tablet formation or said trehalose solids are tabletted as such.

11. Tablets containing crystalline or semi-crystalline trehalose solids containing a crystal type selected from the group consisting of trehalose dihydrate and mixtures of trehalose dihydrate and anhydrous trehalose, and having a specific surface area greater than 0.25 m^2/g, and wherein said tablets have a tensile strength of at least 4 N/mm^2, preferably of at least 5 N/mm^2, more preferably more than 7 N/mm^2.

CER03-0004

Abstract

The current invention relates to direct compressible crystalline or semi-crystalline trehalose solids having a crystal type selected from the group consisting of trehalose dihydrate and mixtures of trehalose dihydrate and anhydrous trehalose, and having a specific surface area of at least 0.25m^2/g. A process for preparing said solids comprises heating a solution of trehalose and applying shear and cooling. The trehalose solids can be applied in food, pharma and cosmetics and tablets prepared from said trehalose solids have improved tensile strength.

Figure 1

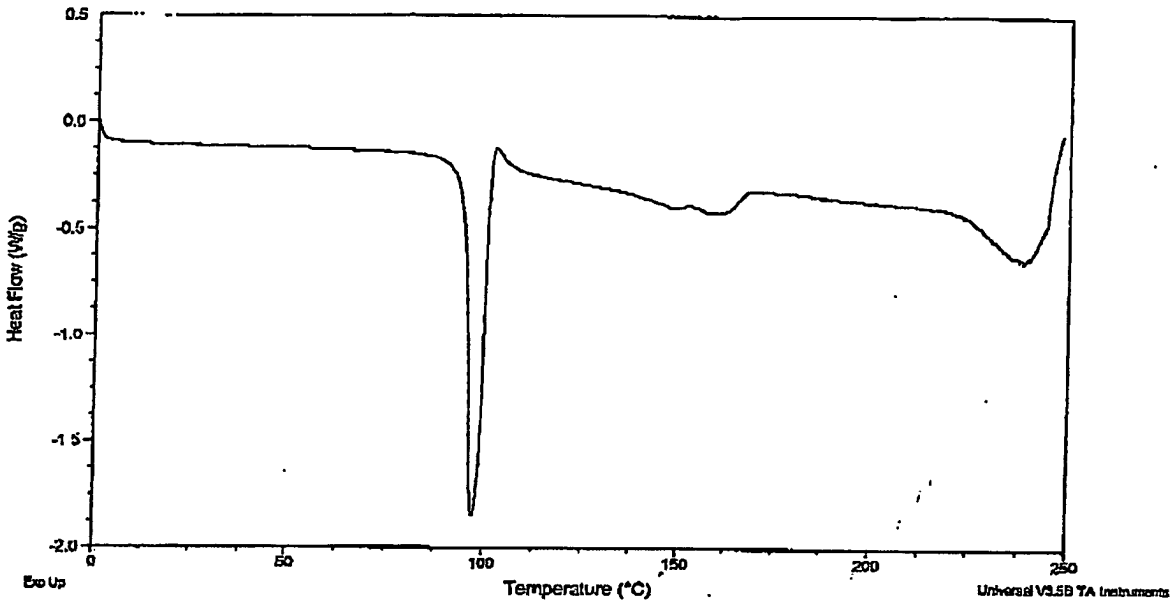

0.5
0.0
-0.5
-1.0
-1.5
-2.0
Heat Flow (W/g)
0
50
100
150
200
250
Exo Up
Temperature (°C)
Universal V3.5B TA Instruments

Figure 2

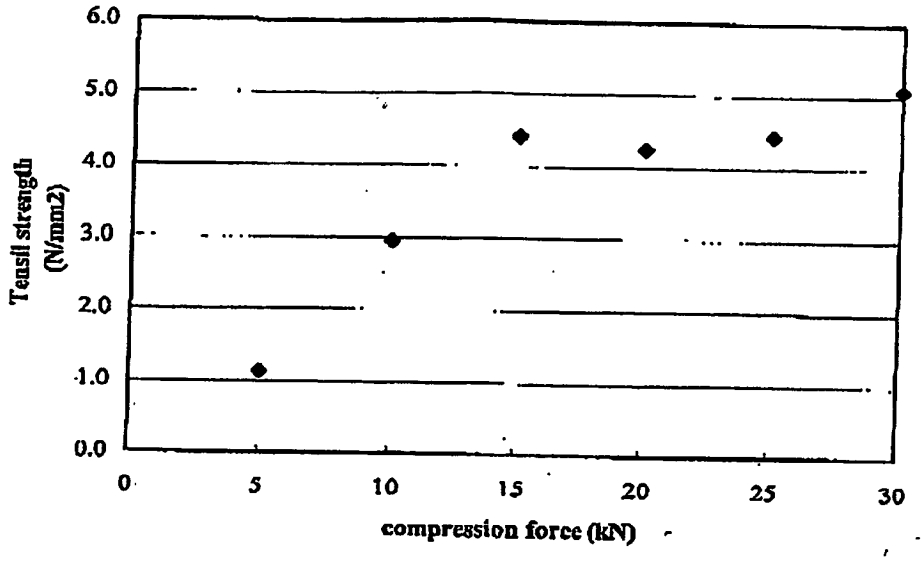
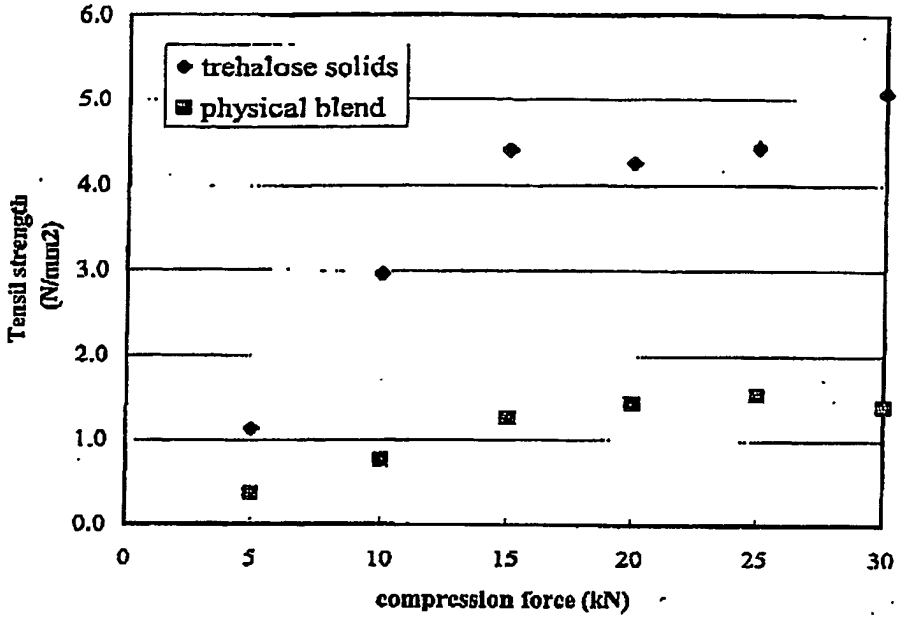

6.0
5.0
4.0
3.0
2.0
1.0
0.0
Tensil strength (N/mm2)
0
5
10
15
20
25
30
compression force (kN)

Figure 3


6.0
5.0
4.0
3.0
2.0
1.0
0.0
Tensil strength (N/mm2)
trehalose solids
physical blend
0
5
10
15
20
25
30
compression force (kN)

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